Influenza Antiviral Resistance: Issues for Consideration
December 19, 2008

Background

- CDC recommends annual influenza vaccination as the first and most important step in preventing the flu.
- Antiviral medications with activity against influenza viruses are a second line of defense against influenza.
- Antiviral medications are important to consider especially for treatment of patients with severe influenza or patients at higher risk for influenza-related complications.
- There are four antiviral medications approved for use in the United States: oseltamivir, zanamivir, amantadine and rimantadine.
    - Oseltamivir and zanamivir have activity against influenza A and B viruses.
    - Amantadine and rimantadine have activity against influenza A viruses, but not against influenza B viruses.
- Influenza viruses can develop resistance to antiviral medications.
- Since 2006, CDC has recommended the use of oseltamivir and zanamivir against seasonal influenza because of a high resistance to amantadine and rimantadine among influenza A (H3N2) viruses.
- In the last two years, CDC has enhanced surveillance efforts for the detection of viruses resistant to oseltamivir (Tamiflu®) and zanamivir (Relenza®).
- These enhanced efforts have provided CDC with the capability to detect resistant strains more quickly, and enabled CDC to monitor for changing trends over time.
- During the 2007-08 influenza season, a small increase in the number of influenza viruses resistant to oseltamivir was observed.
- CDC's influenza season summary for 2007-2008 reported that 10.9% of tested influenza A (H1N1) viruses were resistant to oseltamivir.
- Last season, CDC tested 1,769 viruses for antiviral resistance.
- During the 2007-08 influenza season in the Northern Hemisphere, oseltamivir resistance of H1N1 viruses varied in different countries: from 0% to 70% in some European countries.
- During the 2008 Southern Hemisphere season, oseltamivir resistance of H1N1 viruses continued to be reported, with some Southern Hemisphere countries reporting that a majority of tested A (H1N1) viruses were resistant to oseltamivir.

Current Situation

- At this point in the season, a low level of influenza activity has been reported in the United States. As a result, very few viruses have been available for testing thus far.

Influenza Antiviral Resistance: Discussion Points
(continued from previous page)

- Early and limited data from this season has detected a significant increase in the proportion of influenza A (H1N1) viruses that are resistant to oseltamivir.
- In the latest CDC FluView report published on December 19, 2008, 78 influenza viruses from 15 states had been tested for antiviral resistance.
- This includes 50 influenza A (H1N1) viruses, 8 influenza A (H3N2 viruses) and 20 influenza B viruses.
- Preliminary data show:
    - 49 of the 50 influenza A (H1N1) viruses tested were resistant to oseltamivir (98%).
    - These oseltamivir resistant viruses have been detected in 12 states, but the majority of samples have come from two states.
    - All 50 influenza A (H1N1) viruses were sensitive to zanamivir and amantadine and rimantadine.
    - All 8 influenza A (H3N2) viruses remain sensitive to oseltamivir and zanamivir.
    - All 20 influenza B viruses remain sensitive to oseltamivir and zanamivir.
    - All influenza A(H3N2) viruses tested were resistant to amantadine and rimantadine.
- Weekly reports summarizing U.S. surveillance activity are published every Friday from October through mid-May at http://www.cdc.gov/flu/weekly/fluactivity.htm
- The fact that oseltamivir-resistance is significantly higher among H1N1 viruses compared to last season in the U.S. is not surprising. Worldwide, the proportion of H1N1 viruses that are resistant to oseltamivir has been increasing.
- Influenza viruses change constantly through changes in their genetic makeup, and one of such mutations conferred resistance to oseltamivir.
- There is no evidence that the resistant viruses are causing more severe illness than other influenza viruses or that they are transmitted differently.
- At this time, it's not possible to predict how common H1N1 viruses will be during the rest of the 2008–09 season, as every influenza season is different.
- CDC is monitoring this situation very closely and will continue to test influenza viruses and update information on resistance throughout the influenza season.
- Recommendations regarding the use of antiviral medications have been reviewed and updated guidance will be issued given surveillance data indicating an increase in the number of oseltamivir-resistant influenza H1N1 viruses in the United States.
- Different options for antiviral treatment in the setting of increased circulation of oseltamivir-resistant H1N1 viruses have been considered. These options, such as use of zanamivir or combination therapy with oseltamivir and rimantadine, were outlined in the 2008 influenza recommendations.

Influenza Antiviral Resistance: Discussion Points
(continued from previous page)

- CDC's interim guidance on the use of influenza antiviral medications in the United States for the 2008-09 season will be issued in a Health Alert Advisory on December 19. This revised guidance will be available at www.cdc.gov/flu.

- Clinicians should be aware that revised interim guidance on the use of antiviral medications is being provided by CDC for the current influenza season and will be available at www.cdc.gov/flu.

- Information from local or state virus surveillance data and laboratory testing can help clinicians in selecting appropriate antiviral medications for their patients.

- When influenza A (H1N1) virus infection or exposure is suspected, zanamivir or a combination of oseltamivir and rimantadine are more appropriate options than oseltamivir alone.

- CDC is working to communicate this new guidance broadly through a clinician communications campaign to alert health care providers to the change in recommendations for antiviral medications this season.

- **Influenza vaccines are expected to be effective in preventing or reducing the severity of infection with currently circulating influenza viruses, including oseltamivir-resistant influenza A (H1N1)**